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PULMONARY TUBERCULOSIS: EVOLUTION OF MODERN THERAPY

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FOR more than 25 years the Veterans Administration, the Armed Forces, and the National Tuberculosis and Respiratory Disease Association have held joint conferences to discuss, primarily, the treatment of pulmonary tuberculosis. In January 1972 the conferences were terminated, not because all therapeutic problems had been solved but as a reflection of the declining importance of the disease as a primary cause of death.

At the turn of the century the national death rate from tuberculosis was almost 200 per 100,000; within recent years it has been approximately four per 100,000. Most tuberculosis sanatoria are closed and treatment is now given in general hospitals or on an ambulatory basis. With rare exceptions most physicians do not have the opportunity to treat many cases of active tuberculosis. Of approximately 8,000 admissions to Doctors Hospital, New York, N.Y., in 1971 there were seven cases of tuberculosis, in three of which the disease was active.

ANTIQUITY

The recognition of tuberculosis of the spine in Egyptian mummies

of 3000 B.C. by archeologists[1, 2] in the early 20th century established tuberculosis as one of the oldest diseases known to civilization. Familiarity with consumption by the ancient Hebrews is suggested by several Biblical allusions.[3] In Zechariah the Lord threatened, "Their flesh shall consume away while they stand upon their feet and their eyes shall consume away in their holes."

The literature of ancient Greece contained many references to tuberculosis.[4] In the *Odyssey* Ulysses gave thanks that a grievous consumption did not take his soul from his body. Herodotus, Euripides, Democritus, and Plato indicated a fairly accurate knowledge of the symptoms and clinical course of pulmonary tuberculosis. Aristotle asked philosophically, "Why is it, that those who approach a consumptive patient are stricken with consumption?" His rhetorical answer was that consumption infects the breath, and that those who approach the patient inhale infected air.

The classic Hippocratic descriptions[5] of the tuberculous patient provide ample proof of the prevalence of the disease in the pre-Christian era. For 2,000 years medical students have been taught to look for the emaciated face, the red cheeks, the hoarse voice, the winged shoulder blades, the flat chest, and the curved finger nails. Hippocrates recognized tuberculosis as a common and fatal systemic disease that localized chiefly in the lungs. His patients included many young adults, and his observations led him to conclude that tuberculosis was a contagious disease, the occurrence of which was greatly influenced by hereditary or familial factors. Treatment was simple and related to life in the temples of health. The routine consisted of resting, praying, drinking milk, dieting, exercising, and avoidance of exposure to inclement weather. Drug therapy was not emphasized but various medications were administered palliatively.

The five centuries that separated Hippocrates from Galen added little to the therapy of tuberculosis. The prolific works of Galen[6, 7] included many instructions for the treatment of pulmonary tuberculosis, which was regarded as an ulceration of the lung. Bed rest and quiet were recommended, as were mildly astringent gargles and plasters applied to the chest and head. Red coral, which contains calcium, was prescribed for hemoptysis. The chief item in the diet was milk. The ideal place for cure was Stabiae, on the Bay of Naples, where the air was dry and the cattle were well fed.

Galen was very precise in his advice about diet, favoring such items as the wings and testes of milk-fed cockerels. He also valued coddled eggs and pork, which he eulogized for its effect on weight. In addition to diet the regimen included three baths daily and oil rubs. Galen's strong promotion of Stabiae as a health resort led to the establishment of many houses and inns as residences for patients and their slaves.

The writings of Horace, Ovid, Livy, Seneca, and Celsus contain sufficient references to establish that tuberculosis flourished in ancient Rome.[4] The mass movements of thousands of young warriors during the conquests of the Roman Empire probably contributed to the spread of the disease into adjacent rural communities and countries. The conquests of Rome continued until the tenuous imperialism outside its borders and the decadence from within invited the invasion of barbarian hordes. The Roman Empire declined and fell, and further development of Greco-Roman culture, including medicine, was ended. The Galenic concepts of tuberculosis therapy prevailed for more than 1,000 years.

Premodern Era

It has been thought that tuberculosis was brought to the North and South American continents by Europeans following Columbus' voyages. There is, however, evidence of the prevalence of the disease in North America prior to the European invasion.[8] Jesuit explorers in the early 17th century recorded numerous cases of scrofula and pulmonary tuberculosis in young Indians. Scrofula was common in Europe and readily recognized. In England it was known as "the King's Evil," curable by the royal touch.[9] The Massachusetts Historical Collections contain data stating that consumption was a common cause of death prior to migration by the English. Tuberculosis of the spine was also found in Indian skeletons in Ontario, Canada. There is much evidence of the prevalence of tuberculosis in the English colonies in the 17th century.[10] The Reverend Cotton Mather,[11] famous for his persecution of witchcraft in Salem, also dabbled in medicine. His chief medical work, *The Angel of Bethesda*, spoke of consumption as a very common disease among the English, quoted Galen on therapy, and directed the patient to repent of his sins. For more specific antituberculosis therapy, Mather recommended a concoction obtained by strangling two roosters, beating them to a pulp, boiling them in a mixture of wine and water,

straining through a cloth, and adding to the strained liquid raisins, hartshorn, maidenhair, and saffron.

The 17th century was a golden age of literature, art, philosophy, and science. It was the era of Shakespeare, Milton, Bacon, Molière, Rembrandt, Velasquez, Spinoza, Locke, Descartes, Galileo, and Newton. Medicine, particularly the basic sciences, also participated in this renaissance, and investigators began to discard the opinions of Hippocrates and Galen. Despite the intimate knowledge of tuberculosis and other pulmonary diseases that had developed since antiquity, there was almost no information on either the structure or function of the lungs. The famous Samuel Pepys wrote in his diary on January 22, 1666, that he had just attended a meeting of the Royal Society where respiration was the subject of discussion. His observation was that the participating physicians did not have the vaguest idea of how respiration was performed or what function it had.

In the latter part of the 17th century the gross and microscopic anatomy of the lungs was described by Malpighi and Willis,[12] who discovered that the lung was not a solid structure but consisted of a series of branching tubes ultimately ending in minute air vesicles surrounded by connective tissue and blood vessels. Willis' precise description differentiated between tuberculosis and other wasting diseases loosely described as consumption.

The most famous treatise on tuberculosis in this era was published by Morton[13] in 1689. Its style was pretentious, and its therapeutic recommendations similar to those of the ancients, but the clinical descriptions were accurate. By this time the contagiousness of tuberculosis was generally recognized, and Maynwaringe[14] in 1673 theorized that the infected breath contained invisible particles derived from the diseased lung. Thomas Sydenham[15] suggested that tuberculosis be treated by means of fresh air and horseback riding to agitate the thorax.

The introduction of thoracic percussion by Auenbrugger in the latter part of the 18th century and the invention of the stethoscope by Laënnec in the early 19th century laid the foundations for the establishment of physical diagnosis of the thorax as a routine procedure. Laënnec's studies also established that the tubercle was the anatomic unit of tuberculosis and identified the disease in whatever part of the body it was found. Physical diagnosis was not at once accepted by the medical profession, but the prestige of Jean-Nicholas Corvisart, William Stokes,

and Joseph Skoda—all of whom were well-known teachers—eventually persuaded doctors of the value of this procedure. It thus became possible to detect the disease by examination and to correlate the physical findings with pathologic changes in the lungs.

In the latter half of the 19th century progress in tuberculosis research was accelerated. In 1863 Villemin[16] reproduced tuberculosis in rabbits by injecting tuberculous tissue; thereby he showed that the infecting agent could be transmitted. In 1882 Koch[17] announced the discovery of the tubercle bacillus. Virchow and many prominent clinicians were reluctant to accept the concept of bacteria as causes of disease.[18] The momentous news of Koch's discovery was reported 10 days later in the United States in the *New York World* on April 3, 1882. Roentgen's[19] discovery of the x ray occurred in 1895; he had forgotten to turn off the current in a covered Crookes vacuum tube and noted a green light emanating from the tube. The light had an unusual property: namely, it could penetrate flesh. However, its usefulness in examination of the thorax was hampered by technical difficulties, and it was not until the 20th century that roentgenography of the chest was used routinely for the diagnosis of tuberculosis.[20]

Sanatorium Therapy

It was also in the 19th century that new methods of treatment were introduced to supplement the enriched diets of milk and eggs prescribed in ancient Greece 2,000 years previously. In 1836 George Bodington,[21] a practitioner in Birmingham, England, thought it would be advantageous for tuberculosis patients if they were sequestered in one building, where their diets and physical activities could be supervised while they were constantly exposed to fresh air. His venture failed for lack of support from the medical profession, but it was an idea whose time had come, and others tried it more successfully in succeeding years.[22]

In 1859 Dr. Hermann Brehmer[23] opened a sanatorium for the treatment of pulmonary tuberculosis in Görbersdorf, Germany. It attracted many patients. In addition to accommodations for the patients the establishment provided beautiful parks and gently sloping walks which enabled participation in graduated exercises. Brehmer believed that the combination of mountain air and exercise was most beneficial. In 1868 a young military surgeon, Peter Dettweiler,[24] arrived at the sanatorium after experiencing pulmonary hemorrhages. He was again

called into service in the Franco-Prussian War, and his tuberculosis flared up once more. On his return to Brehmer's sanatorium he came to the conclusion that patients benefitted more from rest than from exercise. In 1876 an opportunity presented itself for him to take charge of a new sanatorium in Falkenstein where he could put into practice his opinions about bed rest.[25]

The widespread growth of the sanatorium movement established tuberculosis as a specialized branch of medicine. Therapy was clearly defined and included bed rest in and out of doors, specialized breathing exercises, and frequent high-caloric feedings. Doctors who came to sanatoria as patients often departed as specialists extolling the advantages of sanatorium life. The emphasis on the salubrious qualities of climate made it obligatory for physicians to send patients to the mountains. The anxiety about the contagiousness of the disease was also an important factor in the creation of municipal and state sanatoria.

Concepts of tuberculosis as a contagious disease date back to antiquity but were generally related to constitutional predisposition. Sylvius,[26] who contributed greatly to the pathology of tuberculosis in the late 17th century, believed that the disease was acquired because of humoral changes. In Italy and in Spain in the 19th century the contagiousness of tuberculosis was accepted and laws were passed requiring destruction of clothing and articles used by the deceased.[27]

The warm, pleasant climate of Italy made it a haven for patients with pulmonary disease, and if they died in their hotels there was a charge of £100 sterling for indemnity. In 1867 the *Lancet*[28] stated that Italian concern for contagion was based on avarice, not science. There was considerable opposition to the contagion theory and its implications in Europe, but the establishment of sanatoria provided a ready solution. The patient was isolated in an institution dedicated to his treatment, and his family and community were no longer threatened by exposure to the disease.

The famous Trudeau Sanatorium in Saranac Lake, N.Y., came into being fortuitously. One late afternoon in the fall of 1868 Edward L. Trudeau,[29] a young New Yorker, was walking up Fourth Avenue toward 23rd street when he noticed a light in the window of the College of Physicians and Surgeons. On a sudden impulse he decided to become a doctor. He entered the building, where he found Dr. Francis Delafield who, at the time, was acting as both pathologist and dean. Trudeau

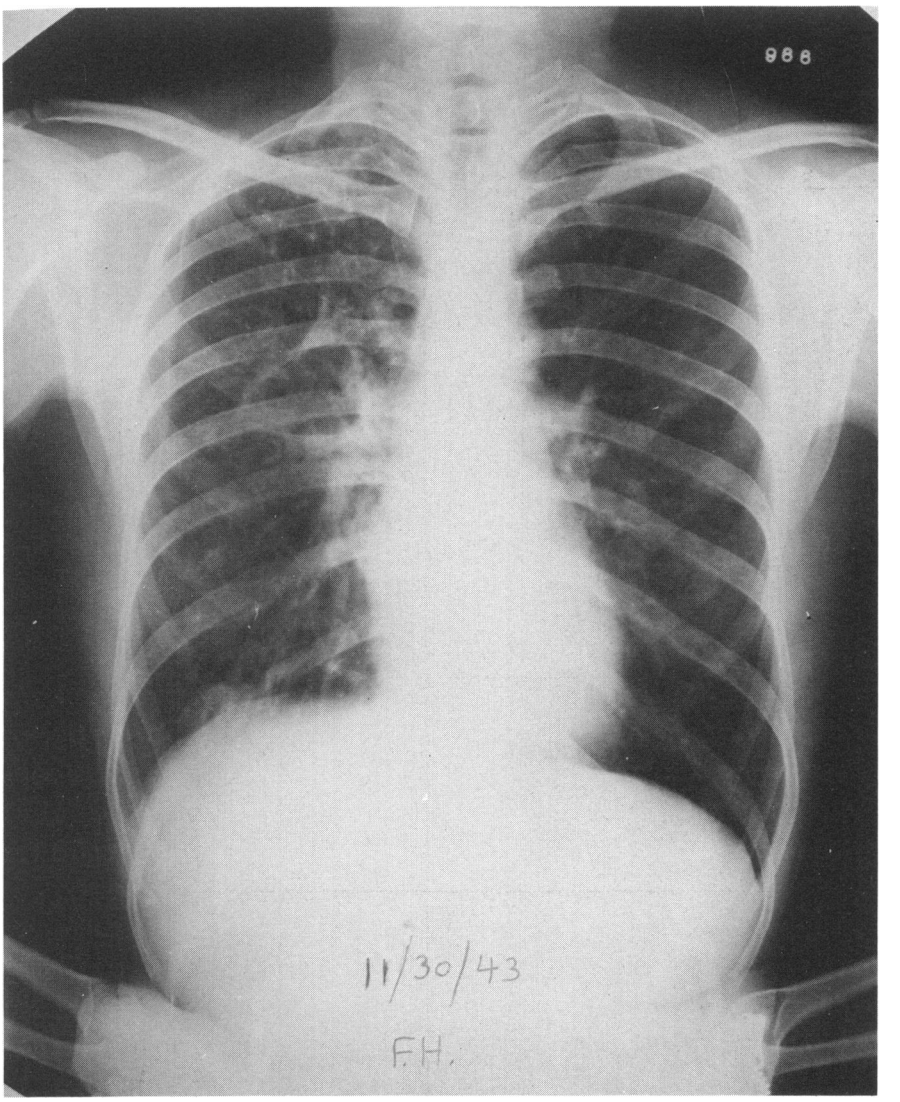

Fig. 1a. X ray of 30-year-old woman showing large cavity in apical segment of the right lower lobe; sputum positive for tubercle bacilli on direct smear.

paid the five-dollar registration fee and was promptly accepted. Shortly after graduation he had recurrent episodes of fever. He consulted the eminent Dr. Edward Janeway, who prescribed horseback riding in a warm climate. The results were disastrous.

On May 25, 1873, Trudeau went up to the Adirondack mountains to die in surroundings that offered peace and contentment. As time passed

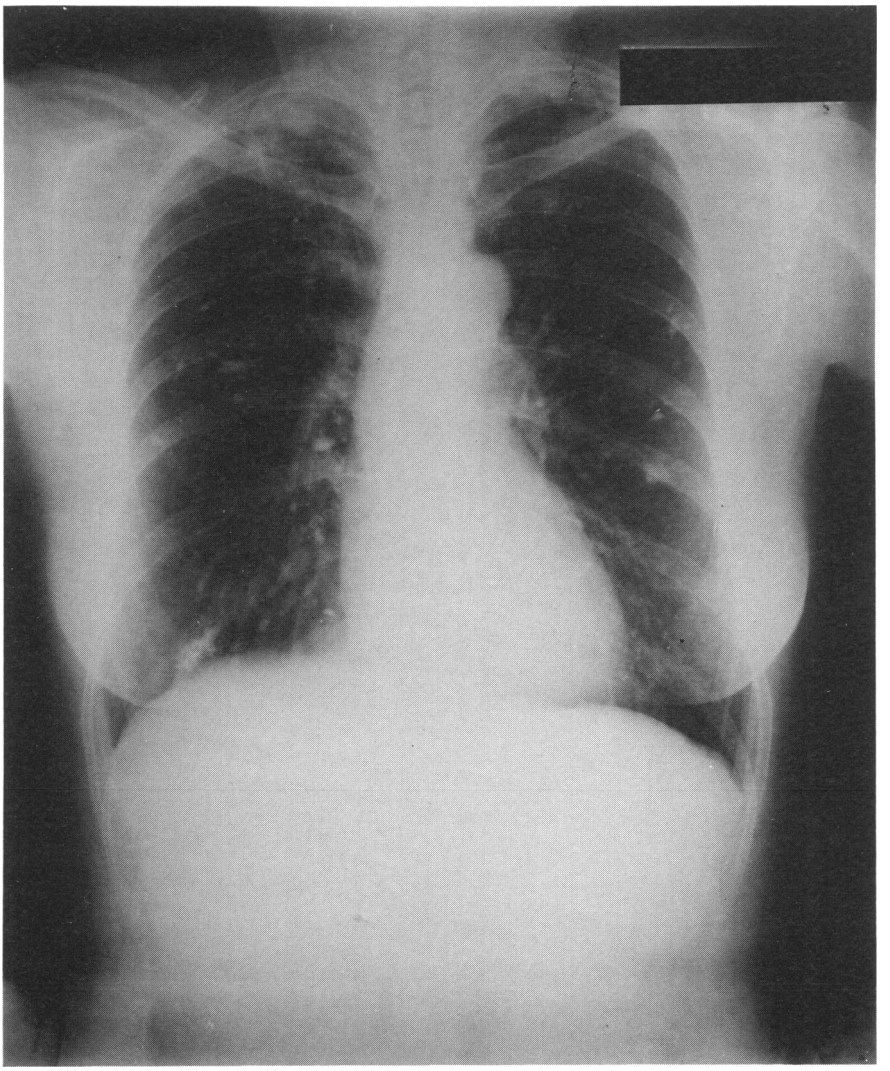

Fig. 1b. X ray of same patient 26 years later showing no evidence of cavitation. Treatment consisted of bed rest in a sanatorium for three years with cavity closure and negative gastric cultures at time of discharge. There were no recurrences.

he gradually improved. He came to the conclusion that the mountain climate was responsible for arresting the disease. He read about the work of Brehmer and Dettweiler and he decided to build a sanatorium in Saranac Lake. With the help of wealthy sportsmen who frequented the area he was able to obtain funds. The first cottage, completed in January 1885, accommodated two patients. Eventually the establishment

became an institution not only for the treatment of tuberculosis but also for teaching and research. Fifty years later there were 600 sanatoria in the United States with a total capacity of 95,000 beds.

As the sanatorium movement expanded, each institution developed its own regulations of therapy.[30] The emphasis on the beneficial effects of the great outdoors led some sanatoria to expose bed patients up to 10 hours daily to all types of weather. Breathing exercises with intricate maneuvers were also introduced, as were respiratory cabinets, cold-water sprays, special diets with feedings between meals, and even artificial radiation (Figures 1a and b).

Concurrent with the recognition of the sanatorium routine by the medical profession as the best method of treating tuberculosis there was also a growing conviction on the part of close observers that rest, fresh air, and diet were of little value for patients who had extensive or cavitary disease. In 1903 Dr. Lawrason Brown[31] of the Trudeau Sanatorium published an analysis of 1,500 cases discharged from two to 18 years previously. Approximately 1,000 patients could be traced, of whom more than half (53.2%) were dead. Of the living patients, less than one third were well. Dr. Brown also culled from the 1,000 cases 366 classified as having incipient disease. Of the 258 patients traced, 170 (66%) were well. Similar observations in other sanatoria[32] led to the development of surgical measures designed to treat cavitary disease more aggressively.

The idea that artificial collapse of the lung might arrest the disease originated with Bourru[33] in Paris in 1774 but it was not given a clinical trial. In 1822 Carson, [34, 35] a physiologist, attempted to induce pneumothorax in two tuberculosis patients and failed. Despite these failures, the concept of specific therapy was intriguing. It was again advocated by McRuer[36] in the United States in 1835 and, at about the same time, by Houghton and Stokes[37] in England. The latter two had been greatly impressed by the improvement that occasionally occurred in the diseased lung after spontaneous pneumothorax. The same observation was made by Toussaint[38] several decades later. In 1885 Cayley[39] induced artificial pneumothorax in a patient who had had a pulmonary hemorrhage. The most important work in the promotion of pneumothorax therapy was reported in 1882 by Forlanini,[40-43] whose apparatus consisted of two connected water bottles, one of which contained nitrogen. When the other bottle was raised, water flowed into the bottle containing nitrogen, forcing the gas through a tube and into a needle inserted into the patient's

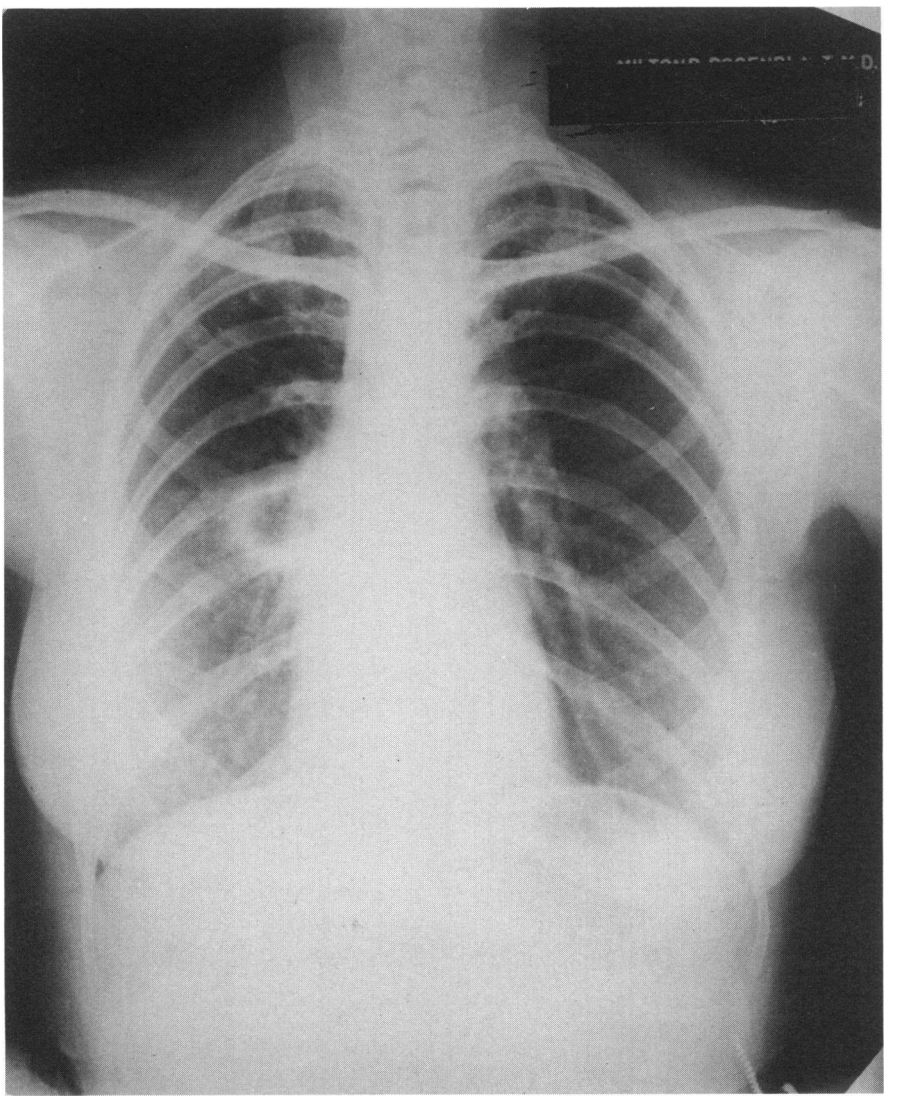

Fig. 2a. X ray of 25-year-old woman with thick-walled cavity in apical segment of right lower lobe; sputum positive for tubercle bacilli on direct smear.

pleural cavity. Forlanini was successful in inducing artificial pneumothorax because, unlike the earlier experimenters, he had penetrated the pleura with a needle rather than a scalpel.

Artificial pneumothorax was also recommended by Dr. John B. Murphy[44] of Chicago at the annual meeting of the American Medical Association in 1898. Murphy apparently had been unaware of Forlanini's

experiments. His interest was based on observations that spontaneous pneumothorax could promote healing, and he had concluded that artificially induced collapse should also be beneficial. At the time of his report Murphy had treated eight patients, using a trocar to gain access to the pleural space.

Dr. Murphy's prestige in the profession resulted in his being deluged with so many requests for treatment that he was compelled to decide whether to become a tuberculosis specialist or to continue as a surgeon. His decision was to continue with surgery, and artificial pneumothorax was relegated to his assistant, Dr. Lemke.[45] The latter, a prodigious worker, by 1902 had treated 350 cases. However, he died in 1906, and with him died all enthusiasm for the treatment. A review of the medical literature up to 1912 revealed only two American contributors on pneumothorax: Murphy and Lemke.

Pneumothorax therapy was revived in the United States by way of Europe. American physicians visiting European clinics prior to World War I were amazed to find that the procedure, promulgated by both Forlanini's work in Italy and Murphy's report of 1898, had become a standard form of therapy for tuberculosis. The prominent European pioneers were Brauer in Germany, Saugman in Denmark, Dumarest and Rist in France, and Lillington in England.[46] When pneumothorax therapy was popularized in the United States it was due largely to the efforts of Hamman, Sloan, Lapham, Floyd, Robinson, Webb, and Balboni.[47] The substitution of air for nitrogen and the introduction of manometers had simplified the technique.[48] By 1915 the treatment became generally known, and between 1915 and 1930 the number of patients receiving pneumothorax increased steadily. In many institutions from one third to one half of all patients admitted had pneumothorax inductions but a national survey[49] revealed that the average incidence was 10%.

The therapeutic limitations of pneumothorax were well known to the profession, but the procedure was widely used until the 1940s. Simplicity of operation and lack of other methods of therapy were probably the main reasons for its continuation. The many complications resulting from this form of therapy ranged from pleural effusion and empyema to cerebral embolism. The main problem was that pleural adhesions and positive intrapleural pressures made it impossible or impractical to maintain the collapse for long periods. A technique introduced by Jacobaeus[50-52] in 1913 for cutting adhesions gained some popularity in

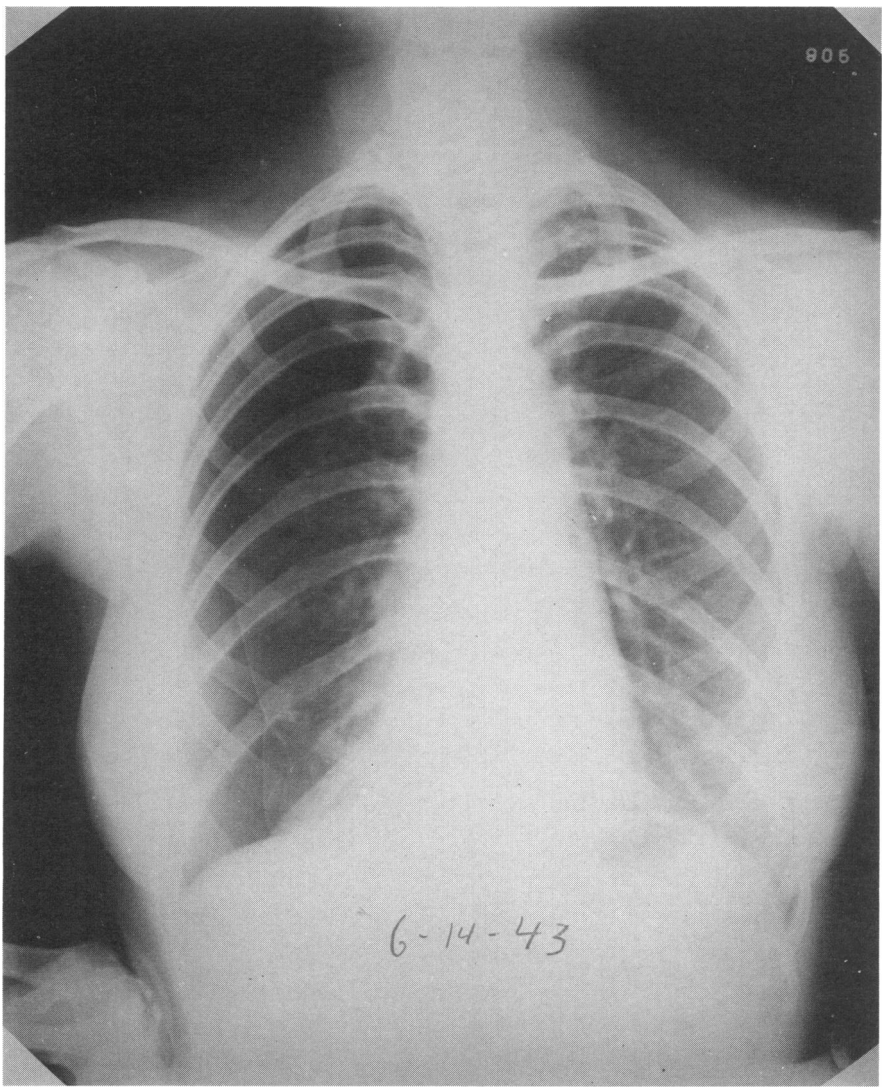

Fig. 2b. X ray seven months after induction of artificial pneumothorax showing about 50% collapse of right lung; sputum negative on culture.

the United States about 20 years later but its usefulness was limited.

The results obtained by pneumothorax treatment differed widely and depended chiefly on the extent of the disease. One institution[53] reported a 44% mortality after two years and another[54] reported a 20% mortality after five years. The fact that patients could resume their former occu-

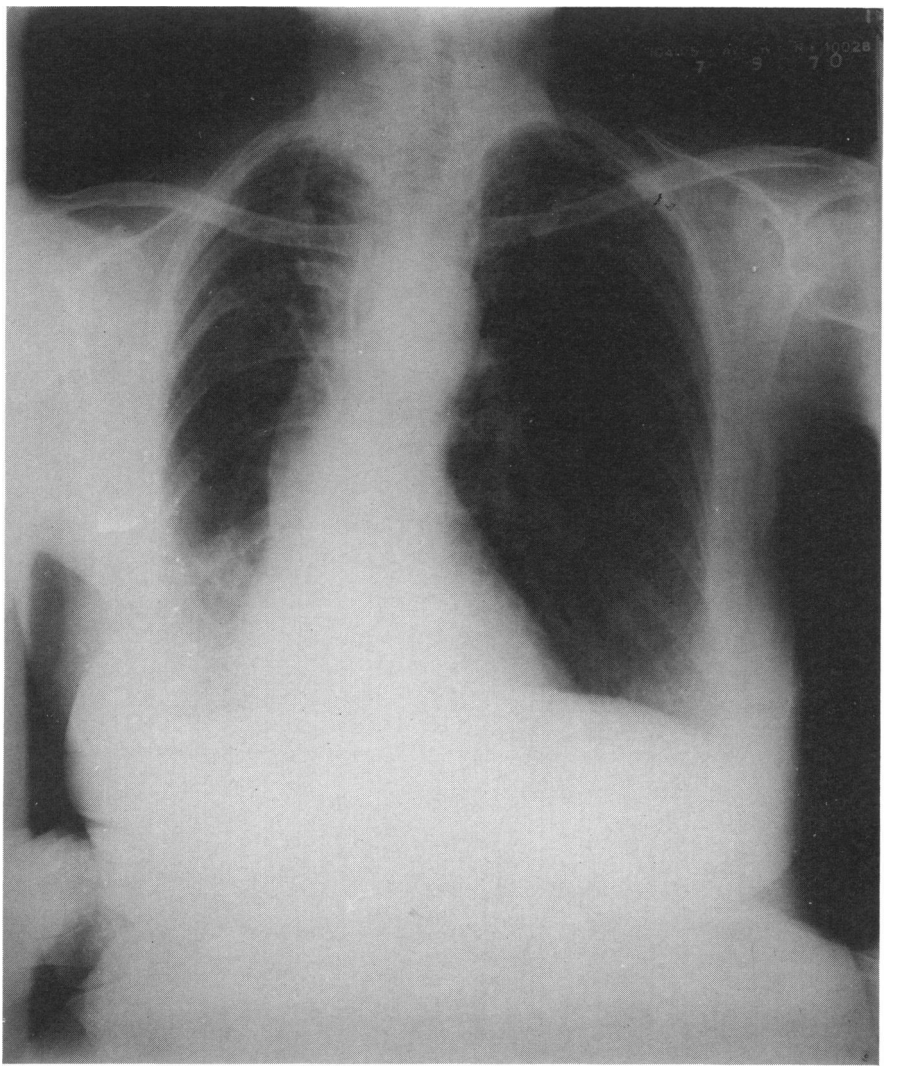

Fig. 2c. X ray 25 years after discontinuance of pneumothorax showing retraction of mediastinal structures to the right and obliterative pleurisy at the base of the right lung; no recurrences.

pations, bear children, and live normally with collapsed lungs dispelled any thoughts about discontinuation of pneumothorax treatment despite its limitations and complications.[55] At the crest of enthusiasm for pneumothorax some physicians were suggesting collapse of healthy lungs to prevent tuberculosis (Figures 2a, b, and c).

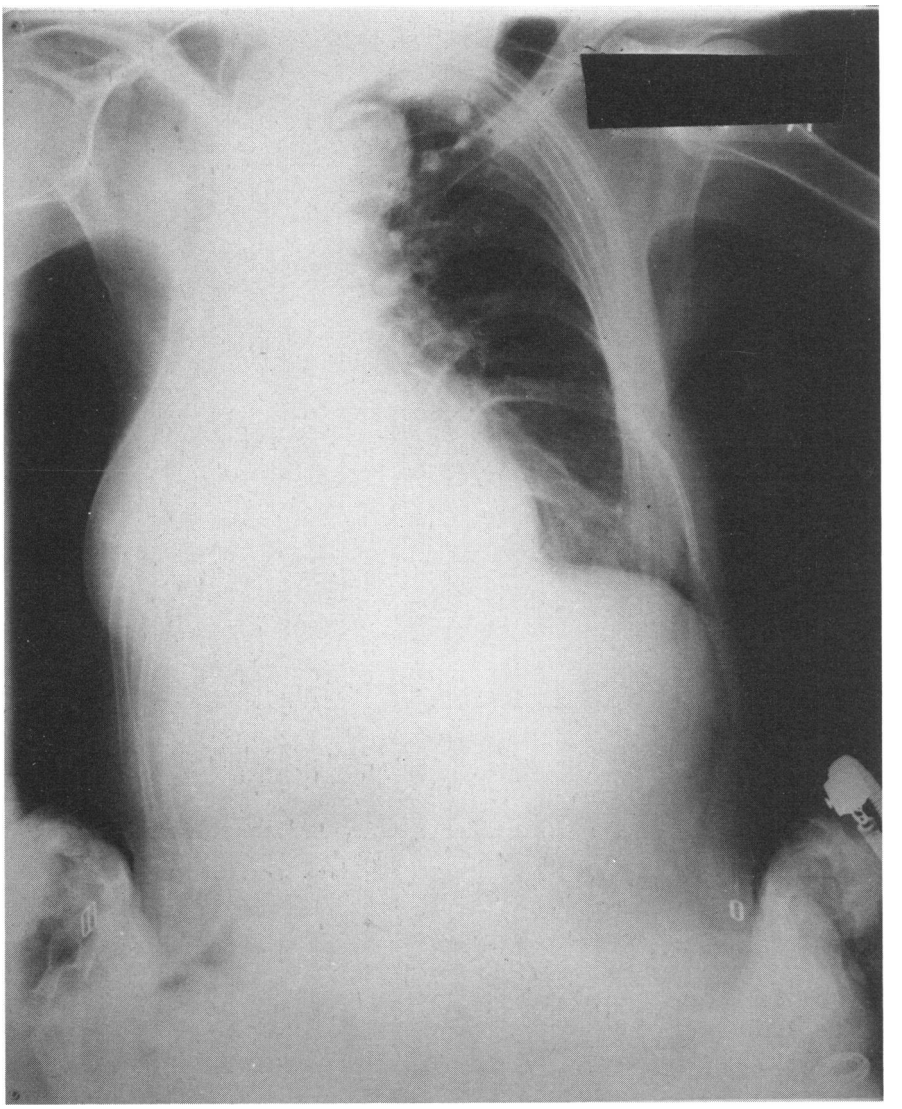

Fig. 3. X ray of 67-year-old woman showing rib deformity produced by three-stage thoracoplasty performed in 1944. There are dense nodular lesions in the left upper lobe. Sputum was converted in 1945 and cultures have been negative for 27 years.

Thoracoplasty

The operation of rib resection to collapse tuberculous cavities was perfected in the late 19th and early 20th centuries. The first thoracoplasty was performed by de Cérenville[56] in 1885. In 1907 Freidrich[57] widely extended the degree of collapse of the lung by removing large

segments of the second to ninth ribs. He further developed the procedure by resecting the first rib also and by leaving the periosteum intact. The latter maneuver enabled the ribs to regenerate and ultimately to provide the patient with a solid chest wall.

In 1909 Brauer[58] introduced a two-stage technique to reduce the surgical shock often encountered in the one-stage thoracoplasty. In 1911 Wilms[59] perfected a technique which permitted greater collapse of the chest wall by resecting the posterior segments of the ribs. This procedure had originally been conceived by Gourdet[60] in 1895 but had been used for treatment of empyema. Wilms and his contemporary, Sauerbach,[61] established the extrapleural paravertebral thoracoplasty as an integral part of the therapy of tuberculosis. The extensive resection of the original technique was later modified by Semb.[62] Thoracoplasty attained its widest popularity in the United States in the 1930s although it was seldom used as a primary procedure. The patient was usually given a trial of pneumothorax and rest; when these failed, thoracoplatsy was considered. This selection of cases was instrumental in the success of the operation. The long waiting period to decide on thoracoplasty eliminated the patients with progressive disease from consideration and provided a residue which consisted of survivors who had demonstrated a certain amount of resistance to the disease.

The purpose of thoracoplasty was to close tuberculous cavities, and it often succeeded. The common complications of the operation were postoperative deformity of the thorax, shrinkage of the operated side, and retraction of the heart and mediastinum. However, the shoulder girdle was not affected, and the thoracic deformity was not apparent in the clothed patient. In properly selected cases the mortality rate was low, and collected sanatorium statistics showed that about 70% of the patients eventually achieved an "arrested" status.[63-66] Postthoracoplasty patients had little difficulty in resuming normal activities (Figure 3).

Ancillary Procedures

Operations to interrupt the function of the phrenic nerve were introduced in 1911 by Stuertz[67] and modified by Sauerbach and Schepelman[68] in 1913, and by Felix[69] and Goetze[70] in 1922. The operation was simple. The purpose was to paralyze the hemidiaphragm, which ascended into the thorax, thereby compressing the diseased lung. The operation was used both as a primary procedure and in cases in which pneumothorax

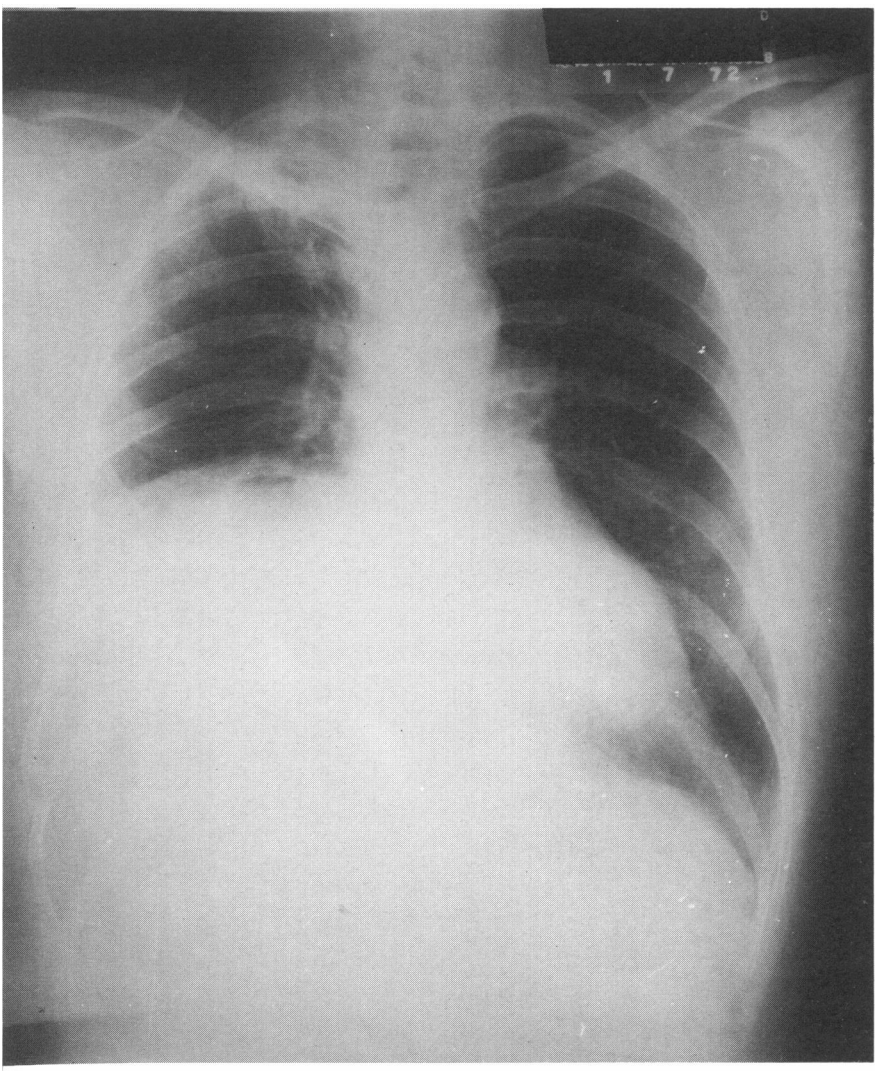

Fig. 4. X ray of 63-year-old man showing elevation of right diaphragm. Phrenicectomy was performed 40 years previously for cavity in right upper lobe. Sputum conversion occurred two months later and there have been no recurrences.

had failed. Phrenicectomy attained a degree of popularity in the United States in the 1930s and early 1940s largely because of the work of John Alexander of Ann Arbor, Mich., who was also a major influence in the promotion of thoracoplasty. In 1946 Banyai[71] published an enthusiastic treatise on pneumoperitoneum which was used in association with phrenicectomy and also as a secondary procedure when pneumothorax

could not be induced or had failed (Figure 4). The injection of air into the peritoneal cavity produced complications similar to those of artificial pneumothorax[72] and the end results were generally unsatisfactory.

Pneumothorax, thoracoplasty, and phrenicectomy attempted to close cavities by compressing the lung or by permitting its elastic tissue to relax. A variety of other intra- and extrapleural procedures were introduced for this purpose. In 1922 Bernou[73] recommended the intrapleural instillation of oil to maintain collapse of the lung. Extrapleural pneumothorax was originally suggested by Mayer[74] in 1913 but was not used until two decades later. The procedure was subsequently modified by insertion of a plombe into the extrapleural space. The operation was called plombage, and the material inserted ranged from fatty tissue[75] to paraffin[76] to lucite balls[77] (Figure 5). An intriguing method of cavity closure was introduced by Monaldi[78, 79] in 1938. The technique was to insert a tube into the tuberculous cavity and apply suction for long peperiods of time in the hope that the cavity would eventually close or decrease in size and be more amenable to collapse by thoracoplasty. Cavity drainage was used sporadically in the United States, with negligible success.

Pulmonary Resection

Resectional therapy of tuberculosis dates back to the animal experiments of Gluck[80] in 1881 and of Bionda[81] in 1883. The first resection in man was performed by Block[82] in 1883. The patient died and at autopsy there was no evidence of tuberculosis. Block shot himself. In 1884 Kronlein[83] resected apical tuberculosis lesions in two patients and both died. One year later Ruggi[84] attempted two resections for tuberculosis; one patient died the next day and the other died nine days later. Profiting from the experiences of his predecessors, Tuffier[85] successfully removed the apical portion of a tuberculous lung in 1891. The patient survived and was presented to the Surgical Congress in Paris five years later as cured.

The first resection for tuberculosis in the United States was performed by Babcock[86] in 1908; he removed the right lower lobe. The patient died two weeks later in the hospital after exposure to a severe storm. Autopsy showed massive caseous tuberculosis of the remaining upper and middle lobes. A few resections were done in the following decades but there were no published accounts until 1935, when Freed-

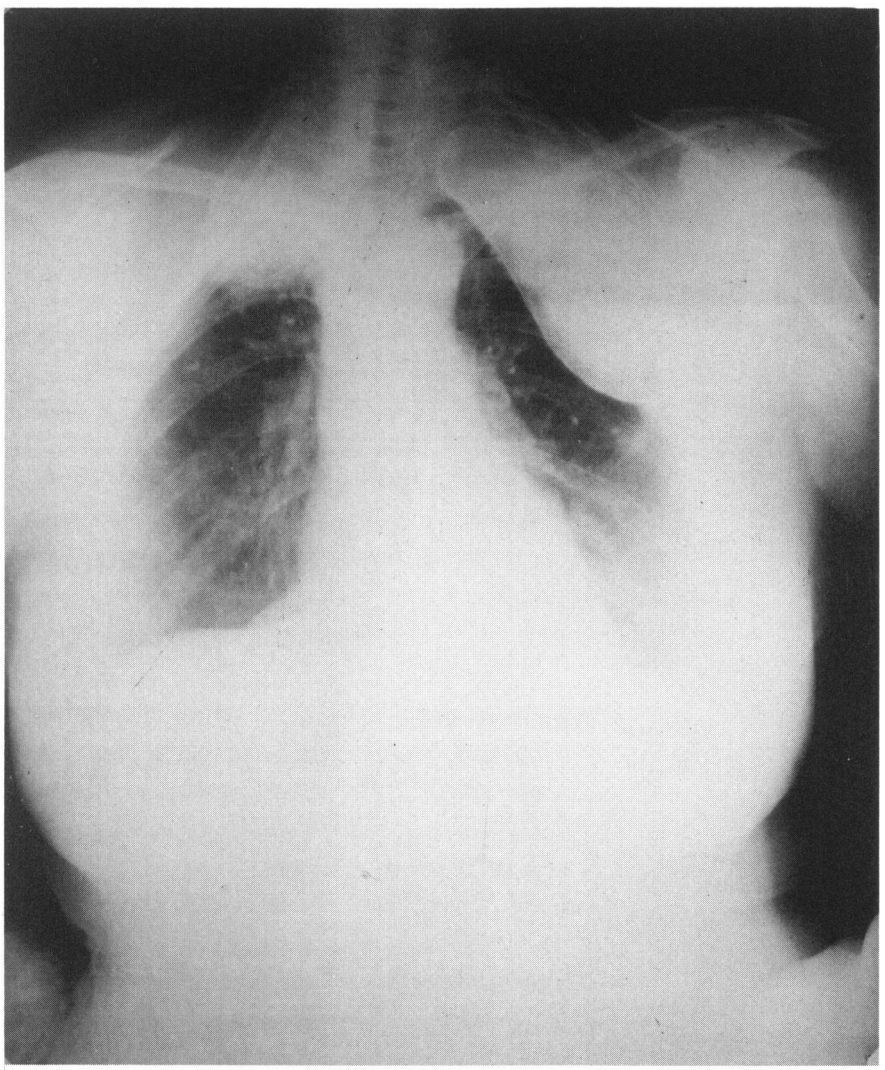

Fig. 5. X ray of 60-year-old woman showing rib resection and density of right apex, the results of right upper thoracoplasty and paraffin plombage. Overlying the left upper lobe is a density produced by oil plombage. Bilateral upper lobe cavitation had been diagnosed 32 years previously and the surgical procedures were completed a year later with sputum conversion; no recurrences.

lander,[87] at a meeting of the American Association for Thoracic Surgery, reported a successful lobectomy for tuberculosis. When the association reconvened five years later it was the accumulated experience that despite advances in technique[88, 89] resection for tuberculosis was

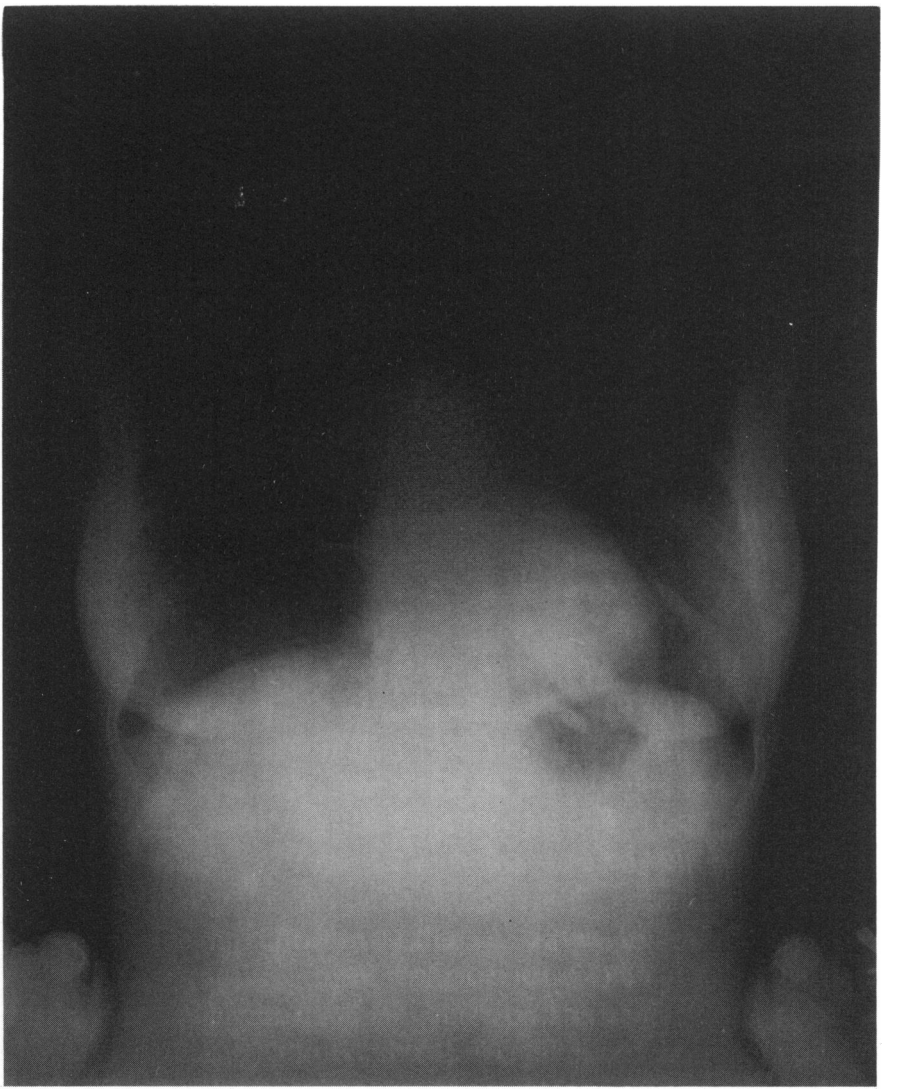

Fig. 6a. X ray of 56-year-old woman showing cavity in right upper lobe. Chemotherapy with streptomycin, INH, and PAS had been started three years previously for bilateral upper lobe cavitation but patient could not tolerate INH and PAS. Later, ethambutol was given but had to be discontinued because of leukopenia. Streptomycin was continued with apparent clearing of lesions but right upper-lobe cavity recurred, as seen on x ray above.

dangerous and was indicated only when other collapse measures had failed.

In 1943 Churchill and Klopstock[90] introduced a new approach to the

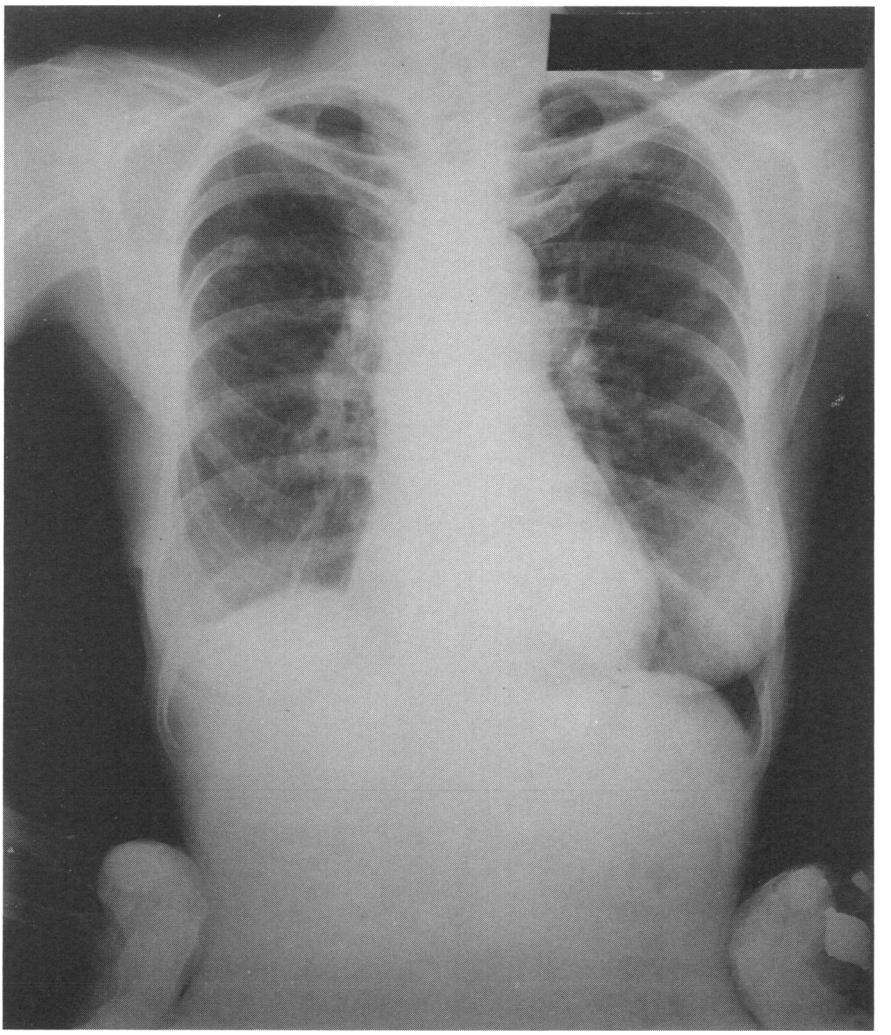

Fig. 6b. X ray 18 months after right upper lobectomy, showing no recurrence of disease. Rifampin and streptomycin were given for three months after operation. Gastric cultures converted two months after operation and have continued negative.

resectional treatment of tuberculosis by redefining the indications and recommending lobectomy as a primary procedure in selected cases. This provided an impetus for further technical perfection and hundreds of patients were operated on during the next few years. An important contribution was made by Chamberlain,[91] who advocated segmental resection inasmuch as the disease was often localized in certain segments of the lung. The administration of streptomycin pre- and postoperatively

reduced the hazards of complications caused by spread of the disease. Since 1950 resectional therapy[92] has been used widely in cases of intractable caseous or cavitary disease, and it has virtually replaced collapse therapy. The dangers of postoperative spread have been largely mitigated by the concurrent use of drugs (Figures 6a and b).[93]

Chemotherapy

Shortly after his discovery of the tubercle bacillus, Koch prepared a glycerine extract of dead tubercle bacilli which he found to have important diagnostic possibilities.[94] He called the liquid tuberculin. The extract's potency in animal experiments suggested that it might have curative properties. The idea was to build up immunity to the disease by a series of injections with gradual increases of dose. The results were often disastrous, but the concept of immunotherapy was intriguing and many physicians used tuberculin during the early decades of the 20th century.[95]

Tuberculin has continued to be used, chiefly as a diagnostic tool. In 1907 von Pirquet[96] introduced the scratch test, subsequently replaced by the Mantoux[97] or intracutaneous test introduced in 1908. Other forms of testing included the conjunctival test, the patch test, and the multiple-puncture test. New methods of purification of tuberculin have been devised; in recent years Purified Protein Derivative has been mostly widely used.[98] In 1921 Calmette[99] suggested that oral administration of attenuated bovine bacilli to infants would confer immunity against tuberculosis before exposure to the disease. The vaccine, popularly known as BCG (Bacillus Calmette-Guerin), was later given by injection. The production of a positive tuberculin reaction was supposed to be the manifestation of immunity. The debate regarding the prophylactic efficacy of BCG continued for decades.

At the turn of the century there was enthusiasm for the injection of dyes such as trypan red, trypan blue, and methylene blue. The theory was that inasmuch as these dyes had an affinity for tuberculous tissue in animal experiments, they would penetrate the diseased areas when injected in humans. When the results were unsuccessful the dyes were combined with iodine and carbolic acid with similar dismal results. Other short-lived cures included creosote, chaulmoogra oil, bile salts, calcium, and glycerophosphates.[100]

The successful results obtained in the treatment of syphilis with

mercury and arsenic inevitably led to the use of these metals in the treatment of tuberculosis. Various salts of copper were also used. The results were uniformly unsuccessful, and this form of therapy aroused little interest in the 20th century. However, treatment with gold salts was popular in the 19th century and during the early decades of the 20th. The therapeutic use of gold is believed to have originated with the Moslems, and Paracelsus included gold in his "elixir of life." The high point in gold therapy came with the introduction of a preparation called sanocrysin by Mollgaard[101] in 1925. The drug was widely used for more than a decade, during which there were many conflicting reports[102] regarding both its toxicity and therapeutic benefits.

The introduction of the sulfonamide drugs in the late 1930s and their apparent antibacterial efficacy led to extensive experimentation to find one or more compounds which could destroy the tubercle bacillus *in vivo*. The drug which appeared to show the most promise was promin.[103] Diasone, promizole, and the thiosemicarbazones[104] were also investigated. After almost a decade of clinical trials it was generally accepted that the sulfone drugs were of little if any value in the treatment of tuberculosis.

The final chapter in the chemotherapy of tuberculosis began with the discovery of streptomycin by Waksman[105] in 1944. Within two years of clinical investigation it became apparent that a definitive treatment of tuberculosis had been found.[106] For several years the drug was controlled and its use restricted to tuberculosis hospitals and sanatoria. The indications for administering the drug and dosage regimens were regulated according to arbitrary criteria based chiefly on studies made in the Veterans Administration hospitals.

When streptomycin became generally available to the medical profession it was found that the drug had a far wider application than was originally anticipated. It was not only curative in patients with exudative forms of pulmonary tuberculosis or ulcerative lesions of the larynx and bronchi but was also beneficial to some degree in chronic fibrocaseous disease. It was also discovered that the drug was equally efficacious when injected intermittently rather than daily. Concurrent with the introduction of lower dosage schedules of two or three times weekly there was a marked reduction in the occurrence of complications such as vertigo. One of the important problems associated with streptomycin treatment was the development of drug-resistant tubercle bacilli. In

some instances this resistance was already present *in vitro* before treatment. This problem has been largely solved since the introduction of other antituberculosis drugs which have been given in combination with streptomycin.

Para-aminosalicylic acid (PAS) was introduced clinically by Lehmann[107] in 1946 for the treatment of intractable thoracoplasty wounds. The use of the drug was prompted by previous investigations by Bernheim,[108] who had found that sodium salts of benzoic and salicylic acid stimulated the metabolism of tubercle bacilli and a derivative was then synthesized which had a catabolic effect.

The bacteriostatic effect of PAS *in vitro* and *in vivo* against tubercle bacilli was further demonstrated by Youmans[109] in 1946 and by Sievers[110] in 1947. In 1949 Block[111] reported its effect in combination with streptomycin. PAS had the advantage of oral administration and was used extensively in conjunction with streptomycin. However, the therapeutic doses were large, and gastrointestinal intolerance was a frequent complication causing premature discontinuance of the drug.

Isoniazid (isonicotinic acid hydrazide) was synthesized in 1912 by Meyer and Mally but was not used as an antituberculous drug until 1951.[112] Experiments with nicotinamides in guinea pigs began in 1944 and were continued with isomers of nicotinic acid. In 1951 several laboratories conducted large-scale studies on the antituberculosis activity of isoniazid in animals; the results were uniformly successful.[113, 114] Clinical experiments were also started in 1951 by Hoffmann-La Roche, Inc., in cooperation with Edward Robitzek and Irving Selikoff at Sea View Hospital, Staten Island, N. Y., and by E. R. Squibb and Sons in cooperation with Walsh McDermott and Carl Muschenheim at The New York Hospital.

The original preparation produced by Hoffmann-La Roche was iproniazid (Marsilid). Later the two pharmaceutical companies independently developed isoniazid. The Bayer Company, in Germany, had also been experimenting with the drug during the same period in cooperation with Philipp Klee at Elberfield. By 1952 it was generally apparent that isoniazid was of definitive therapeutic value[115] and news media showed photographs of patients dancing in the aisles. The drug has been used in combination with streptomycin and PAS. It is inexpensive and well tolerated, and there have been relatively few complications.

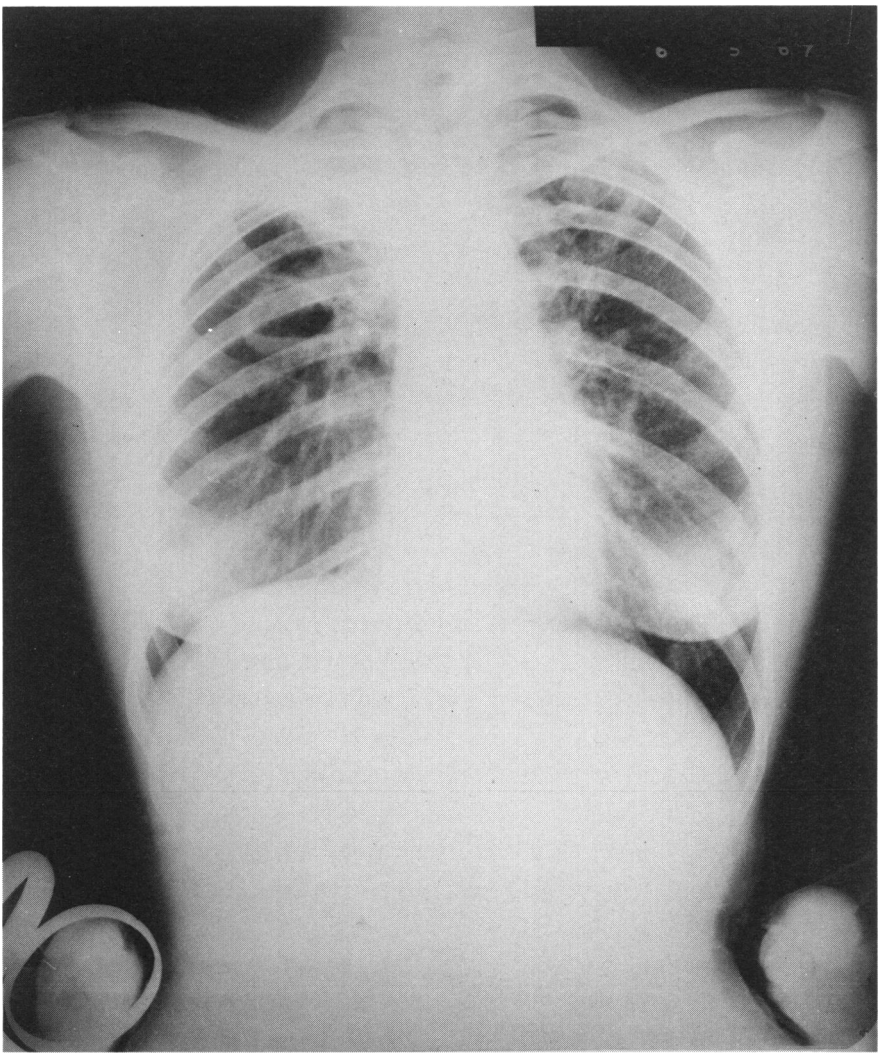

Fig. 7a. X ray of 30-year-old woman showing cavity with fluid level in right upper lobe and infiltrations in left upper lobe.

The prevalence and emergence of drug-resistant tubercle bacilli[116] made it obligatory to continue the search for additional antimicrobial compounds. In 1961 experiments with mice showed that ethambutol[117] was active against strains of *M. tuberculosis* resistant to both streptomycin and isoniazid and was also effective in combination with these drugs. Clinical evaluation was initiated by Lederle Laboratories later in 1961, the drug being marketed under the name of Myambutol. Reports

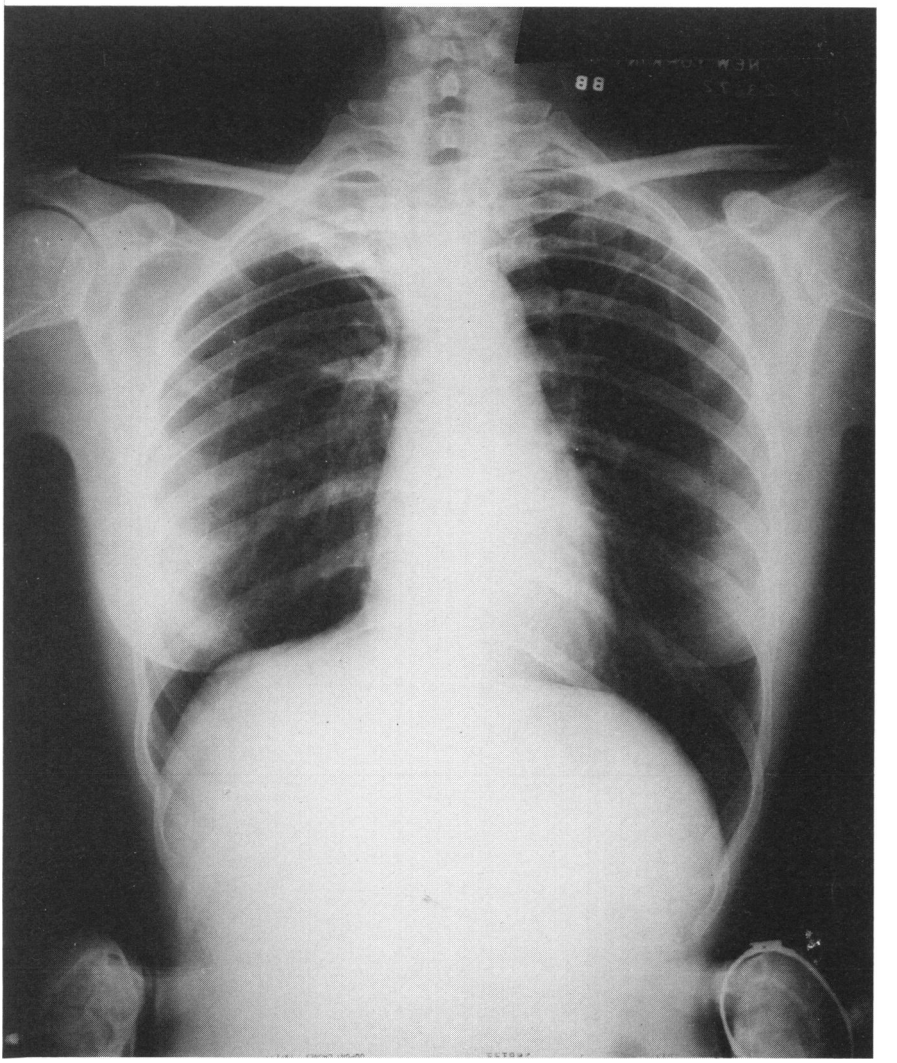

Fig. 7b. X ray five years later, showing fibrotic lesions only in the upper lobes. Patient was treated with streptomycin, INH, and PAS for almost three years. Cultures converted six months after onset of therapy.

since then have been generally favorable,[118] particularly in cases requiring retreatment.[119] The only major side effect reported has been decrease in visual acuity reversible on discontinuation of the drug.

Experiments with the precursors of rifampin were started in 1957 and reported in 1959 at the *Seventh International Symposium on Antibiotics*.[120] The original group of drugs were known as rifamycins, and

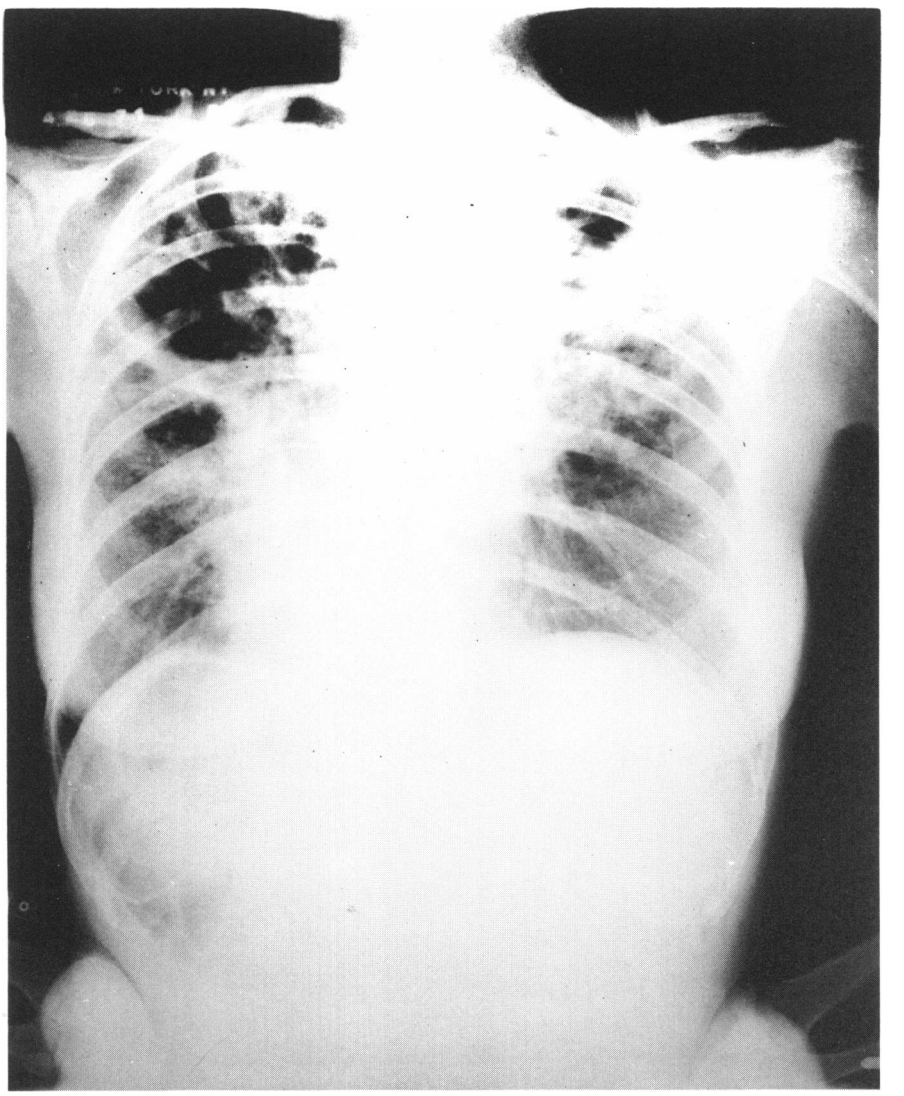

Fig. 8a. X ray of 35-year-old woman with giant cavity replacing the major part of the right upper lobe and multiple smaller cavities in the left upper lobe. There is also a dense infiltration in the right middle and lower lobes.

the development of rifampin followed chemical modification during the next few years.[121] The drug has been found effective against a variety of microorganisms, including tubercle bacilli which are highly susceptible, but resistant strains may emerge rapidly.[122] The oral administration, relative absence of side effects, and clinical effectiveness have made rifampin

very useful in retreatment cases[123] in combination with other antituberculosis drugs. A variety of other drugs were introduced following the discovery of streptomycin and isoniazid to combat resistant tuberculosis. These included cycloserine, ethionamide, kanamycin, pyrazinamide, viomycin, and capreomycin (Figures 7a and b, and 8a and b).

Rehabilitation

One of the far-reaching effects of chemotherapy was the conversion of tuberculosis from a way of life to a disease amenable to therapy. The chronicity of tuberculosis had required long periods of sanatorium care usually extending into years. The patients, mostly young, created their own world of camaraderie. Medical checkups were tolerated as interruptions in the routine of euphoric sanatorium life. Patients whose disease became worse were transferred to hospitals elsewhere. For those who remained there was entertainment, social contact, and romance in idyllic surroundings that blocked out thoughts of the future.

The postsanatorium period was a trying one in the life of the patient. In the early decades of the 20th century about 50% had relapses within two years of discharge.[124] In later years the percentage was reduced but the factors responsible for relapse were never fully understood. Overwork and anxiety were usually blamed but the obvious reason was that the criteria for discharge were inadequate. This became apparent subsequently with the wide use of tomograms, bronchoscopy, and gastric culture. The fear of relapse created an attitude of dependency on social agencies and clinics and provided little encouragement for the patient to give up the way of life that had begun when the diagnosis of tuberculosis was first made.

Shortly after World War I various rehabilitation centers[125] were established to cope with the problem. Each had its own objectives but the basic principle was that the treatment of tuberculosis did not terminate with arrest of the disease. In New York City the Altro Work Shops gave former patients wages and subsidies, and permitted them to work in the factory on a limited schedule of hours depending on their pulmonary condition. During the remainder of the working day the patients rested under supervision. On recommendation of the examining physician the working hours were gradually increased. The patients maintained their own homes and reported for work daily. Rehabilitation usually required from six months to a year and the

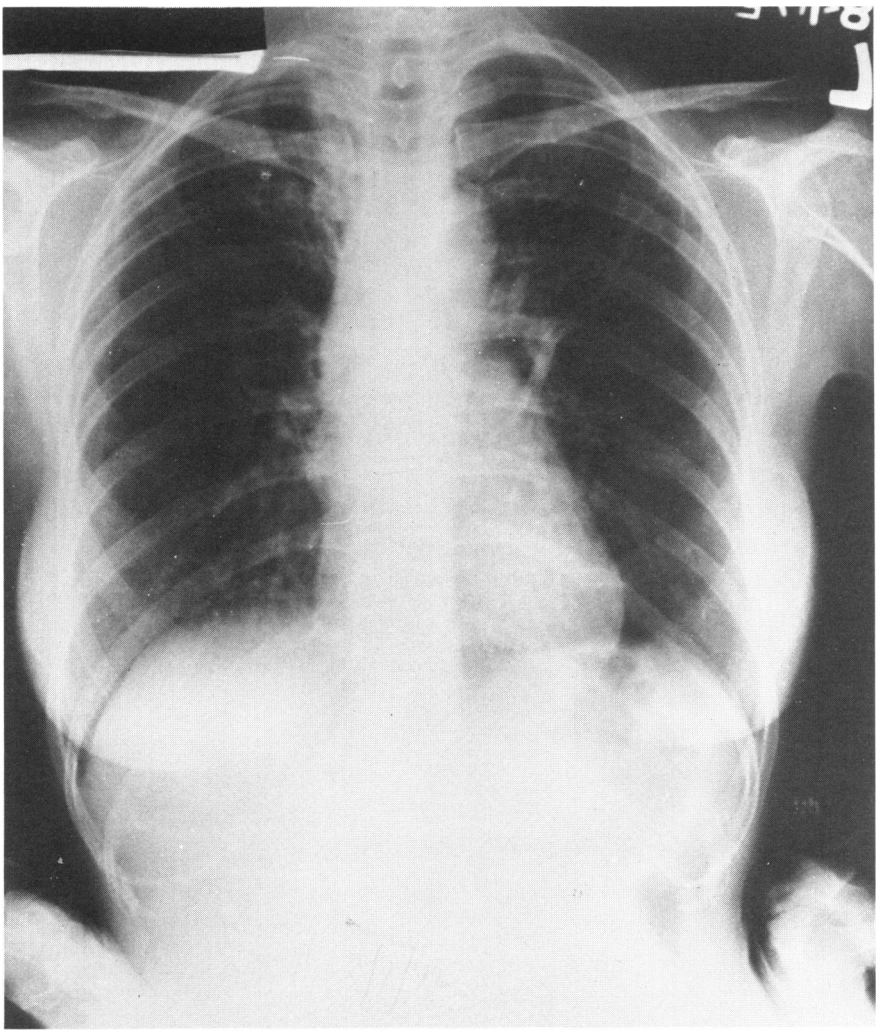

Fig. 8b. X ray 16 months later, showing no evidence of cavitation after treatment with streptomycin, INH, PAS, and ethambutol. Cultures became negative after six months of therapy, which is being continued.

patients were graduated as skilled workers in the manufacture of hospital uniforms and laboratory coats.

An entirely different scheme for rehabilitation was developed in Papworth Village Settlement near Cambridge, England. It was the intention of Dr. Varrier Jones, the originator, to care for tuberculosis patients permanently. The settlement consisted of a hospital and sanatorium section, industrial plants, and a residential area. Patients dis-

charged from the sanatorium were selected for the industrial plants on the basis of pulmonary status and capacity to adapt to communal life. A variety of products was manufactured so that the unskilled workers could be taught simple operations. At first the patients lived in cabins or chalets, and when they reached a work tolerance of six hours they were assigned to cottages as their permanent homes. Unmarried patients lived in dormitories.

Another rehabilitation center, Preston Hall, a settlement for ex-servicemen near London, began as a permanent shelter but ultimately changed its objective to graduation of patients to normal existence in five years. There was a center in Appisberg, Switzerland, which worked in cooperation with sanatoria and hospitals in Zurich. Patients were taught a variety of occupations and graduated when they attained full-time schedules. Other rehabilitation centers established after World War I included an industrial colony in Zonnestrael, Netherlands, in which the patients lived in hostels and cottages and worked in the manufacture of tools, boats, and bicycles. In New Castle, Ireland, the Peamont Sanatorium maintained a rehabilitation workshop which manufactured gloves. Scattered throughout the United States were many smaller rehabilitation centers such as the Potts Memorial Institute in upper New York State, and many less known, sheltered workshops in Saranac Lake, Boston, Hartford, Lake Tomahawk in Wisconsin, and Glen Lake in Minnesota.[126, 127]

Mortality Trends

The decline in tuberculosis mortality began many decades before the advent of sanatoria, isolation regulations, case reporting, tuberculosis associations, and definitive therapy. There are no national vital statistics for the early 19th century, but available records[128] indicate that the tuberculosis death rate for cities such as New York, Boston, Philadelphia, and Baltimore averaged 500 per 100,000 of population. National statistics for the start of the 20th century gave a rate of 200 per 100,000, falling to 150 per 100,000 in 1910. Inasmuch as this great reduction in mortality occurred during an era devoid of any significant antituberculosis measures it is apparent that other factors were responsible.

The 19th century was a time of urbanization. Close contact provided the surroundings for the spread of the disease and death of sus-

ceptible individuals. Those who did not succumb or were not infected were resistant. Whatever the nature of that resistance, it was transmitted to the offspring. With each succeeding generation, more susceptible individuals were eliminated, leaving behind a relatively resistant stable population. Tuberculosis within a given population eventually changes its fundamental aspects with respect to type of disease, severity, and mortality.[129, 130]

In 1930 the death rate from tuberculosis was 71 per 100,000; since then it has declined to four per 100,000. The past four decades have witnessed remarkable strides in therapy. In recent years chemotherapy has resulted in arresting the disease in cases with extensive bilateral cavitary involvement and restoring patients to normal activity in relatively short periods of time. However, the millennium is still not in sight. The incidence of new active cases is still too high. In New York City, in 1969, the new case rate was 36.4 per 100,000 and 79.7 per 100,000 in the low-income, high-density areas. Of the 2,397 new active cases discovered in 1969, two thirds were already moderately or far advanced.[131]

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